

## Exacerbações de Doença Pulmonar Obstrutiva Crónica num Serviço de Medicina Interna: Caracterização e Preditores de Prognóstico

### *Chronic Obstructive Pulmonary Disease Exacerbations in an Internal Medicine Ward: Characterization and Outcome Predictors*

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#### Resumo

**Introdução:** Em Portugal, a doença pulmonar obstrutiva crónica (DPOC) afeta 14,2% daqueles com mais de 40 anos. A Medicina Interna tem um papel nos cuidados da exacerbação de DPOC hospitalizada. O nosso objetivo foi caracterizar as admissões por DPOC exacerbada num Serviço de Medicina Interna focando os preditores de mau prognóstico.

**Métodos:** Um estudo observacional retrospectivo recolheu dados de três anos consecutivos. Para a análise univariada e multivariada foi assumido o evento morte intra-hospitalar por qualquer causa.

**Resultados:** A amostra integrou 280 casos. A média das idades foi de 76,0 anos e 53,6% eram homens. À admissão, a depressão do estado de consciência foi evidente em 21,8% e hipotensão em 3,6%. Detectou-se acidemia em 36% e hipercapnia em 64,3%. Hemoglobina abaixo de 10,0 g/dL verificou-se em 4,6%, eosinopenia em 20,4%, e creatininemia superior a 2,0 mg/dL em 6,0%. Dez por cento tinham fibrilhação auricular. Vinte e nove doentes faleceram no hospital (10,4%). Identificámos os seguintes preditores: admissão nos 90 dias prévios (OR 4,7;  $p = 0,006$ ), fibrilhação auricular (OR 5,0;  $p = 0,002$ ), pressão sistólica < 100 mm Hg (OR 3,7;  $p = 0,023$ ), eosinopenia (OR 2,7;  $p = 0,034$ ), anemia (OR 5,1;  $p = 0,026$ ) e disfunção renal (OR 3,8;  $p = 0,048$ ). A ausência de preditores na admissão correspondeu a um perfil de baixo risco.

**Conclusão:** Comparado com a generalidade dos doentes com exacerbação com DPOC, aqueles admitidos num Serviço de Medicina Interna tendem a ser mais idosos e a ter mais comorbilidades. Os preditores identificados têm relação com a fisiopatologia da exacerbação da DPOC.

**Palavra-chave:** Doença Pulmonar Obstrutiva Crónica/complicações; Hospitalização; Medicina Interna; Prognóstico.

#### Abstract

**Introduction:** In Portugal, chronic obstructive pulmonary disease (COPD) affects around 14.2% of those older than 40 years. Internal Medicine plays a role in the hospitalized COPD exacerbation patient care. Our objective was to characterize the COPD exacerbation patients admitted to an Internal Medicine ward focusing on adverse outcome predictors.

**Methods:** An observational retrospective study retrieved data from three consecutive years. A univariate and multivariate analysis was performed assuming the all-cause in-hospital death outcome.

**Results:** The sample comprised 280 cases. The mean age was 76.0 years and 53.6% were male. At admission, depressed mental status was evident in 21.8% and hypotension in 3.6%. Thirty six percent were acidemic and 64.3% were hypercapnic. A hemoglobin value below 10.0 g/dL was found in 4.6%, eosinopenia in 20.4%, and creatinine above 2.0 mg/dL in 6.0%. Ten percent had atrial fibrillation. Twenty-nine patients died in the hospital (10.4%). We identified the following predictors: admission in the previous 90 days (OR 4.7;  $p = 0.006$ ), atrial fibrillation (OR 5.0;  $p = 0.002$ ), systolic blood pressure < 100 mm Hg (OR 3.7;  $p = 0.023$ ), eosinopenia (OR 2.7;  $p = 0.034$ ) and hemoglobin < 10 g/dL (OR 5.1;  $p = 0.026$ ) and creatinine > 2.0 mg/dL (OR 3.8;  $p = 0.048$ ). Absence of predictors at admission was linked to a low risk profile.

**Conclusion:** Compared to the overall COPD exacerbation patient, those admitted to an Internal Medicine tend to be older and to have higher degree of comorbidity. The identified predictors can be linked to the COPD exacerbation pathophysiology.

**Keywords:** Hospitalization; Internal Medicine; Prognosis; Pulmonary Disease, Chronic Obstructive/complications.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory disease responsible for a significant decline in life expectancy and quality of life of those afflicted by it. In Portugal, it affects 14.2% of those older than 40 years. In 2013, the number of hospital admission derived from COPD was 8361 and the in-hospital mortality was 7.4%.<sup>1</sup> Exacerbations of COPD are recognized as important events in the natural disease course: repeated exacerbations accelerate the disease progression, lead to quality of life deterioration and, when associated with ventilatory failure, to premature death.<sup>2</sup> The approach to COPD exacerbation patient includes therapy prescription and health care resources allocation according to severity.<sup>3</sup> Outcome predictors specific for COPD exacerbation were identified in the critical care context.<sup>4</sup> Another study found a different set of outcome predictors (like acidemia, eosinopenia and atrial fibrillation) but excluded patients who required long term domiciliary ventilation or afflicted by considerable survival-limiting comorbidities.<sup>5</sup> In our daily practice in an Internal Medicine ward, we often deal with patients in these circumstances adding those with high degree of dependence. These facts may shift the COPD exacerbation profile in our wards from that found in Pulmonology wards, respiratory care, and critical care units. This study aims to characterize the admissions caused by acute exacerbations of COPD in an Internal Medicine ward, and, secondarily, to identify parameters known at the time of admission associated with in-hospital outcome.

## Methods

In order to achieve that objective, an observational retrospective study was designed and the institution ethics committee approval was obtained. Clinical records from consecutive admissions to an Internal Medicine ward between January 2011 and December 2013 were reviewed. The inclusion criteria were: clinical diagnosis by the attending physician of acute exacerbation of COPD leading to hospital admission; admission from the community; previous diagnosis of COPD supported by spirometric evidence (forced expiratory volume in first second / forced vital capacity ratio lower than 0.70 without significant improvement after bronchodilation) when clinically stable; patient age equal or superior than 18 years. The exclusion criteria were: concurrent diagnosis at admission (including stroke, acute heart failure, acute coronary syndrome, pulmonary embolism, and thoracic trauma) based on attending physician judgment and/or confirmatory exams. Patients with comorbidities expected to limit survival at 12 months, submitted to domiciliary oxygen/ventilation or having 'do-not-intubate' order were not excluded. Socio-demographic (gender, age) and COPD-related characteris-

tics (active or past smoking habits, spirometric results, last spirometry date) prior to the admission were taken. Clinical status and complementary exam results at the admission were collected. The clinical status contained Glasgow coma scale, systolic blood pressure, heart rate, respiratory rate, and temperature. The selection of parameters from arterial blood gasimetry, hemogram and biochemical study was based on the readiness in our emergency room and on the clinical relevance reported in the consulted literature.<sup>3-5</sup> Parameters with more than 5% of missing values were excluded from the analysis. Depressed mental status was defined as Glasgow coma scale inferior to 15 points. Hypotension was defined systolic blood pressure lower than 90 mm Hg. Acidemia was defined as arterial pH lower than 7.35 and hypercapnia as arterial pCO<sub>2</sub> higher than 45 mm Hg. Eosinophil count inferior to  $0.5 \times 10^9/L$  denoted eosinopenia. The diagnosis of atrial fibrillation (AF) required documentation on 12-lead electrocardiogram at the time of hospital admission. Further data concerning the in-hospital therapy (pharmacologic therapy, mechanical ventilation need) or and clinical outcomes (complications, intensive care unit admission, and all-cause in-hospital death) were also assessed. The characterization of the patient sample included proportions (count and relative frequency), and means with standard deviation.

A comparison of variables between the survivor to discharge and deceased in hospital groups was performed. After assuring normality status with Shapiro-Wilk test, independent sample Student t or Welch-Satterthwaite test, according to Levene's test for equality of variance, were used to compare the continuous variable means. For categorical variables we used Fisher exact test. To assess the predictive factors, we selected parameters with differences between groups according to a p value below 0.10 criterion. This maximizes the selection of potential predictors and parallels previous studies with similar methodology.<sup>5</sup> Variables were reformatted to dichotomic type using cut-off points identified according to: visual inspection of the receiver operator characteristic (ROC) curve; a clinically relevant value; a mean. Then a binary logistic regression model for the in-hospital death outcome was elaborated. The final model performance was evaluated by measuring the area under predicted probability versus verified outcome ROC curve, model Nagelkerk  $R^2$  and Hosmer and Lemeshow goodness-of-fit test  $\chi^2$ .

Finally, patients were distributed according to number of predictive factors to assess the effect of cumulative presence on group mortality.

All data was accessed only by the authors using the institution electronic process application. The statistical analysis was performed using IBM SPSS® version 19. A p value below 0.05 was assumed as statistically reliable.

**Table 1:** Characteristics description of the patient sample, and comparison between survivor and deceased groups (clinical background and admission status)

Variable	Total*	Survived to discharge*	Died in hospital*	t test (df)	p value <sup>†</sup>
	n = 280	n = 251	n = 29		
Background					
Male	150 (53.6%)	134 (53.4%)	16 (55.2%)	-	0.507
Age (years)	76.0 ± 10.0	75.5 ± 10.6	80.8 ± 6.8	-3.7 (45.5)‡	0.001
Charlson index	5.0 ± 1.2	4.9 ± 0.9	5.2 ± 1.7	1.5 (278)§	0.131
Cerebrovascular disease	78 (27.8%)	69 (27.5%)	9 (31.0%)	-	0.691
Ischemic heart disease	77 (27.5%)	67 (26.7%)	10 (34.4%)	-	0.400
Arterial hypertension	115 (41.1%)	102 (40.6%)	13 (44.8%)	-	0.663
Diabetes <i>mellitus</i>	46 (16.4%)	41 (16.3%)	5 (17.2%)	-	0.901
Chronic kidney disease	39 (13.9%)	34 (13.5%)	5 (17.2%)	-	0.586
Cognitive impairment	36 (9.3%)	32 (12.7%)	4 (13.7%)	-	0.879
Active or past smoking habits	100 (35.7%)	89 (35.5%)	11 (37.9%)	-	0.471
Admission in the previous 90 days	26 (9.3%)	19 (7.6%)	7 (24.1%)	-	0.010
FEV1 (% predicted)	53.6 ± 17.0	53.4 ± 16.5	54.4 ± 17.3	0.3 (278)§	0.759
FCV (L)	2.1 ± 0.8	2.1 ± 0.8	1.9 ± 0.8	-1.3 (278)§	0.204
Last spirometry dating > 2 years	92 (32.8%)	80 (31.9%)	12 (41.4%)	-	0.303
“Do-not-intubate” order	97 (34.6%)	85 (33.9%)	12 (41.4%)	-	0.418
Home medication					
Long-action β-agonist	159 (56.8%)	141 (56.2%)	18 (62.1%)	-	0.344
Anticholinergic	128 (45.7%)	117 (46.6%)	11 (37.9%)	-	0.246
Inhaled corticosteroid	137 (48.9%)	122 (48.6%)	15 (51.7%)	-	0.451
Xantines	81 (28.9%)	71 (28.3%)	10 (34.5%)	-	0.309
Systemic corticosteroid	17 (6.1%)	16 (6.4%)	1 (3.4%)	-	0.455
Long term oxygen	104 (37.1%)	93 (37.1%)	11 (37.9%)	-	0.538
Admission clinical status					
Glasgow come scale < 15	61 (21.8%)	56 (22.3%)	5 (17.2%)	-	0.531
Systolic blood pressure (mm Hg)	130.0 ± 26.0	131.1 ± 26.0	120.0 ± 28.0	2.0 (33.9)‡	0.048

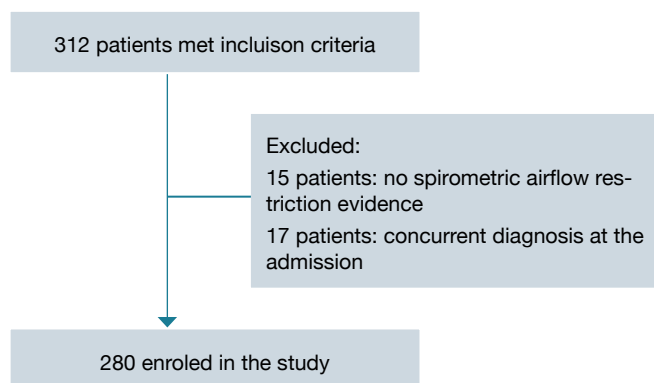
Respiratory rate (per minute)	26.0 ± 6.3	25.9 ± 6.1	27.2 ± 7.0	1.1 (278)§	0.278
Temperature (°C)	36.9 ± 0.5	36.8 ± 0.6	36.9 ± 0.7	0.8 (278)§	0.406
Admission ABG					
pH	7.37 ± 0.9	7.37 ± 0.1	7.35 ± 0.1	1.2 (34.6)‡	0.250
pCO2 (mm Hg)	56.1 ± 18.6	56.2 ± 18.7	54.9 ± 18.5	0.4 (278)§	0.712
pO2-fiO2 ratio	240.5 ± 77.1	239 ± 73.0	245 ± 105.0	-0.3 (31.2)‡	0.790
Bicarbonate (mmol/L)	29.1 ± 6.3	29.0 ± 6.0	30.0 ± 6.5	0.8 (278)§	0.400
Lactate (mmol/L)	1.5 ± 1.3	1.4 ± 1.2	1.8 ± 1.8	-1.0 (32.6)‡	0.249
Admission lab work					
Leucocyte count (10 <sup>9</sup> /L)	12.0 ± 5.3	12.0 ± 5.2	11.4 ± 6.2	0.5 (32.9)‡	0.608
Neutrophil count (10 <sup>9</sup> /L)	9.6 ± 5.1	9.7 ± 5.1	8.8 ± 4.8	0.8 (35.5)‡	0.389
Lymphocyte count (10 <sup>9</sup> /L)	1.5 ± 1.6	1.4 ± 1.1	1.9 ± 3.7	-0.7 (28.5)‡	0.475
Neutrophil-lymphocyte ratio	11.5 ± 11.7	11.4 ± 11.1	12.2 ± 15.9	-0.3 (31.3)‡	0.786
Eosinophil count (10 <sup>9</sup> /L)	0.9 ± 0.8	1.1 ± 0.8	0.7 ± 0.5	2.5 (47.0)‡	0.013
Hemoglobin (g/dL)	13.5 ± 1.9	13.5 ± 1.9	12.7 ± 2.3	2.1 (278)§	0.041
Hematocrit	41.3 ± 6.3	41.5 ± 6.1	38.6 ± 7.2	2.5 (278)§	0.041
RDW	15.5 ± 2.3	15.5 ± 2.4	15.6 ± 1.6	0.3 (278)§	0.794
Creatinine (mg/dL)	1.17 ± 0.4	1.1 ± 0.4	1.3 ± 0.6	-2.1 (278)§	0.035
C reactive protein (mg/L)	86.3 ± 89.0	85.1 ± 95.1	96.4 ± 121	-0.5 (32.0)‡	0.631
Atrial fibrillation on ECG	30 (10.7%)	21 (8.4%)	9 (31.0%)	-	<0.001
Pseudomonas aeruginosa isolation	5 (1.7%)	4 (1.6%)	1 (3.4%)	-	0.524
Other MRM isolation	3 (1.1%)	3 (1.2%)	0 (0.0%)	-	0.554

\*Continuous variables presented as mean ± standard deviation and categorical variables as count (frequency %). ‡ 2-tailed significance of the t test for continuous variables or Fisher exact test for categorical variables. ‡ Welch-Satterthwaite t test. § Student t test. df - degrees of freedom. FEV1 – forced expiratory volume in one second. FVC – forced vital capacity. ABG – arterial blood gasimetry. RDW – red cell distribution width. ECG – electrocardiogram. MRM – multi-resistant microorganisms: methicillin-resistant *Staphylococcus aureus*, extended spectrum beta-lactamase Gram negatives

## Results

The inclusion criteria were met in 312 cases. Documented spirometric evidence of airway flow resistance was not found in 15 cases and 17 cases had a concurrent diagnosis at admission (Fig. 1). The remaining 280 cases were enrolled in the study. The mean age of the patients was 76.0 ± 10.0 years, and 53.6% were male participants. Tables 1 and 2 show the characteristics of the patient sample. Depressed mental status was evident in 21.8% and hypoten-

sion in 3.6%. Thirty six percent were acidemic and 64.3% were hypercapnic. Of the seven complications (2.5%) encountered, five (1.8%) were nosocomial pneumonia and two (0.7%) were acute pulmonary edema. Respiratory failure aggravation lead to 10 critical care unit admissions (3.6%). Twenty nine patients died (10.4%). The 48-hour mortality was 2.9% (eight patients) and 7-day mortality 6.1% (17 patients). Uremia, glicemia, ionogram were excluded due to frequent missing values.



**Figura 1:** Flowchart of patient disposition

Comparing survivor and deceased groups, differences were found in the following parameters known at admission: age, hospital admission in the previous 90 days, systolic blood pressure, eosinophil count, hemoglobin, hematocrit, creatininemia, and atrial fibrillation (Table 1). A more frequent requirement for mechanical ventilation, intensive care unit admission and a higher rate of complications were found in the deceased group. According to the described methodology, the following dichotomic variables were included in a logistic regression model for in-hospital death outcome: older than 80 years (104 cases – 37.1%), hospital admission in the previous 90 days (16 cases – 5.7%), hemoglobin below 10.0 g/dL (13 cases – 4.6%), hematocrit inferior to 44% (13 cases – 4.6%), creatinine above 2.0 mg/

**Table 2:** Characteristics description of the patient sample, and comparison between survivor and deceased groups (therapy and outcomes)

Variable	Total*	Survived to discharge*	Died in hospital*	t test (df)	p value†
		(n = 251)	(n = 29)		
Hospital therapy					
Inhaled bronchodilator	280 (100%)	251 (100%)	29 (100%)	-	1.000
Systemic corticosteroid	280 (100%)	251 (100%)	29 (100%)	-	1.000
Oxygen	270 (96.4%)	241 (96.0%)	29 (100%)	-	0.418
Antibiotic	250 (89.3%)	224 (80.0%)	26 (89.6%)	-	0.244
Noninvasive ventilation	119 (42.5%)	102 (40.6%)	17 (58.6%)	-	0.050
Invasive mechanical ventilation	11 (3.9%)	7 (2.8%)	4 (13.8%)	-	0.018
Vasopressor	1 (0.4%)	1 (0.4%)	0 (0.0 %)	-	0.896
Outcomes					
ICU admission	10 (3.6%)	7 (2.8%)	3 (10.3%)	-	0.073
Hospital stay length (days)	7.9 ± 5.0	7.8 ± 4.7	7.9 ± 7.7	-0.1 (30.4)‡	0.960
Complications	7 (2.5%)	4 (1.6%)	3 (10.3%)	-	0.004
In-hospital death	29 (10.4%)	-	-	-	-

\*Continuous variables presented as mean ± standard deviation and categorical variables as count (frequency %). † 2-tailed significance of the t test for continuous variables or Fisher exact test for categorical variables. ‡ Welch-Satterthwaite t test. df - degrees of freedom. ICU – intensive care unit.

**Table 3:** Predictors of all-cause in-hospital death after logistic regression analysis

Variable	Unadjusted odds ratio	B	Wald Chi-square (df)	2-tailed <i>p</i> -value	Adjusted odds ratio
Atrial fibrillation	5.8	1.9	12.9 (1)	0.002*	5.0
Admission in the previous 90 days	3.8	1.6	7.9 (1)	0.006*	4.7
Hemoglobin < 10 g/dL	3.8	1.7	5.1 (1)	0.026*	5.1
Creatinine > 2.0 mg/dL	4.5	1.4	4.0 (1)	0.048*	3.8
SBP < 100 mm Hg	3.9	1.3	5.1 (1)	0.023*	3.7
Eosinophil count < 0.5 x 10 <sup>9</sup> /L	2.2	1.0	4.7 (1)	0.034*	2.7
Age > 80 years	2.6	0.7	2.91 (1)	0.078	2.2

\**p* value was statistically reliable. df - degrees of freedom. SBP – systolic blood pressure.

**Table 4:** Patient distribution according to number of identifiable predictive factors and respective mortality

Number of predictive factors	All patients	(n = 280)	Excluding DNIO patients	(n = 183)
	Cases n (%)	Deceased n (%)	Cases n (%)	Deceased n (%)
0	152 (54.3%)	3 (2.0%)	102 (55.7%)	0 (0.0%)
1	94 (33.6%)	12 (12.8%)	60 (32.8%)	9 (15.0%)
2	29 (10.4%)	11 (37.9%)	15 (8.2%)	5 (33.3%)
3	6 (2.1%)	3 (50.0%)	6 (3.2%)	3 (50.0%)
≥4	0 (0.0%)	-	0 (0.0%)	-

DNIO – do-not-intubate order.

dL (17 cases – 6.0%), SBP lower than 100 mm Hg (26 cases – 9.3%), eosinophil count higher than 0.5 x 10<sup>9</sup>/L (57 cases – 20.4%), presence of AF (Table 3). Patients showing AF at admission were 5.0 times more likely to die in the hospital. Those with hemoglobin below 10.0 g/dL faced similar odds. Having a hospital admission in the preceding 90 days, creatinine above 2.0 mg/dL, SBP lower than 100 mm Hg or eosinopenia at the admission was associated with the in-hospital death outcome in lesser extent. We could not find an association between age and the outcome.

Hemoglobin and hematocrit produced redundant results. The presence of both predictors did not improve the model so hematocrit was excluded. The model Nagelkerk *R*<sup>2</sup> was 0.288. The Hosmer and Lemeshow goodness-of-fit test had  $\chi^2 = 4.2$  (5) and *p* = 0.584. There were no assumptions violation and none of the small number of statistical outliers significantly influenced the model. The area under the ROC of predicted versus verified outcomes was 0.827.

Finally, a match in accumulation of predictive factors and increase of deceased frequency was detected. (Table 4).



## Discussion

Our analysis considered patients who were primarily treated in an Internal Medicine ward and included those with 'do-not-intubate' order and/or survival-limitative comorbidities to better represent the circumstances which internist doctors face every day. Comparing our results to similar studies, we noticed: our patients were older and the frequency of cardiovascular, cerebrovascular and kidney failure was higher, corresponding a greater comorbidity index mean; ambulatory spirometric results were worst; long term oxygen prescription was more frequent; a lower frequency of prescribed  $\beta$ 2-agonist and systemic corticosteroid was evident; regarding the clinical status at admission, they were more tachycardic and more hypotensive on average; higher frequency of acidemic patients, renal dysfunction and lower levels of hemoglobin/hematocrit was detected; even though a greater requirement for mechanical ventilation was observed, the overall all-cause in-hospital mortality was comparable.<sup>5-7</sup>

In our patient sample, the factors that most contributed to in-hospital death were: hospital admission in preceding 90 days, hemoglobin below 10.0 g/dL, creatinine above 2.0 md/dL, SBP below 100 mm Hg, eosinophil count lower than  $0.5 \times 10^9/L$  and presence of AF.

The concomitant presence of COPD and cardiac arrhythmia, including AF, is common and several architectural and electrophysiological changes are known to occur in the right heart of COPD patients.<sup>8</sup> Some authors concluded that reduced lung function is an independent predictor for incident AF and appointed hypoxia and cor pulmonale as physiopathologic intermediaries to some extent.<sup>9</sup> Likewise, the manifestation of AF may heighten the oxygen demand in a hypoxic/acidemic status of COPD exacerbation leading to further cardiac function compromise. Furthermore, AF increases the risk of embolization events.<sup>10</sup> These events could justify our results where AF had a direr impact on in-hospital outcome. Similar findings were reported previously.<sup>5</sup> The other cardiovascular parameter associated with in-hospital death was systolic blood pressure below 100 mm Hg. Hypotension could be a result of a decreased cardiac output derived from a failing left ventricle (acidemia and hypoxia) or from lower venous return as the intra-thoracic pressure builds up due to air trapping and dyspnea. Intravascular depletion due to tachypnea, fever or iatrogenic diuresis could also result in hypotension. Analogous findings were attested by other authors.<sup>11</sup>

Being ubiquitous as a prognostic marker in several chronic diseases, the need for repeated hospital admissions could signal a rapid decline in the patient status, an increase in disease severity and/or surrounding comorbidities and an inability to mitigate the symptoms with domiciliary therapies.<sup>2</sup> This supports the admission in the preced-

ing 90 days variable as a negative predictive factor.

Hemoglobin level inferior to 10.0 g/dL was the next predictive factor found. Indeed, the COPD patients who required hospitalization had an increased frequency of anemia as stated in two 2006 studies.<sup>12,13</sup> In another study regarding patients with respiratory acidosis submitted to noninvasive mechanical ventilation, anemia was associated with in-hospital death.<sup>14</sup> The same conclusion was evident in COPD patients admitted to critical care units.<sup>4</sup> We hypothesize that anemia could diminish the oxygen delivery to vital organs, added to the burden of respiratory insufficiency. Moreover, anemia may represent a marker of malnutrition or chronic disease, heralding a worst prognosis.

Classic acute phase markers like leukocytosis with neutrophilia or elevated C reactive protein did not sign a bad outcome. Instead, our data revealed eosinopenia as a negative predictive factor. Other studies point to the same conclusion.<sup>5</sup> The eosinophil count was appointed as a useful marker of severity in patients admitted with an exacerbation of COPD leading to more mortality and lengthier hospital stay.<sup>15</sup> Eosinopenia was reported in acute inflammation pathophysiology studies.<sup>16</sup> And it can indicate a hastened inflammatory response as shown in critical care patients.<sup>17</sup> In our analysis, other hematologic markers like neutrophil-lymphocyte ratio or red cell distribution width could not be associated with patient outcome.

Our results could not correlate the presence of acidemia or hypercapnia with a worst outcome. In investigations considering exclusively 'do-not-intubate' order patients, pH level alone was also incapable of predicting in-hospital death.<sup>18</sup> But some authors suggest these markers as a severity factor leading to this outcome.<sup>5</sup> More recent studies signal compensatory mechanisms impairment as the underlying aggravating factor and not the acidemia per se, and those patients require more ventilation support and had worst outcome.<sup>19</sup> An important compensatory mechanism lies in kidney bicarbonate production. Indeed, our results indicate kidney failure herald a worst prognosis. Other studies pointed similar findings.<sup>11</sup> The renal impairment can debilitate the bicarbonate production and deteriorate the excretion of acidic compounds, producing metabolic acidosis in addition to respiratory acidosis and leading to an even more unfavorable outcome.<sup>19</sup> Critical respiratory acidosis at admission may had hasten mechanical ventilation (invasive or noninvasive) justifying the similitude between the groups as is ground knowledge that type 2 respiratory failure with respiratory acidosis calls for those treatments.<sup>20,21</sup> The same can be applied to results concerning the depressed level of consciousness. So, considering the in-hospital death outcome, pharmacologic and ventilatory therapy failure may represent a more adequate prognostic marker.

Age was considered an outcome predictor in two studies.<sup>5,22</sup>

In our results, albeit there was a difference between groups, an age-outcome association was not statically significant in the final regression model. In regression intermediary steps that excluded the hemoglobin and creatinine level parameters, age above 80 years became significant. Therefore, age may represent a surrogate marker since anemia and renal compromises were more frequent in older patients. A higher age could represent a more advanced disease and greater conjunction of comorbidities.

Parameter's odds ratio presented by the regression analysis varied from 2.0 to 5.1 suggesting a high degree of association with the outcome. Furthermore, the ROC curve also points an important link between expected and verified outcome, and the mortality raised according to predictors accumulation. This knowledge could assist in distinguishing low/high risk patients at the time of the admission. We can conjecture the usefulness of repeated parameter evaluation during the hospital stay as a pathophysiologic assessment tool. Moreover, identified parameters, like low blood pressure, low hemoglobin level, renal dysfunction or AF presence, may represent intervention targets in the COPD exacerbation management alongside respiratory dysfunction focused therapies.

We recognize certain limitations adding to the retrospective nature of the study. The patient selection relied on convenience sampling and was restricted to Internal Medicine ward admissions from the community. This limits results generalization to other clinical contexts like ambulatory or critical care units. This also inhibits the usage as out/inpatient selection criteria. Certain parameters that could not be measured in all the subjects, justified by different attending physician criteria or restrains due to institution policies, and were not included in the analysis. Some could, hypothetically, strengthen the prediction model. More studies are needed to attest the feasibility of these outcome predictors.

## Conclusion

Compared to the overall COPD exacerbation patient profile, those admitted to an Internal Medicine ward have specific characteristics as they tend to be older and to have more comorbidities. We found adverse outcome predictors: admission in the preceding 90 days, cardiovascular (atrial fibrillation and hypotension), hematologic (eosinopenia and anemia) and renal dysfunction. Although these markers do not immediately relate to respiratory dysfunction (like hypercapnia or acidemia), they can be linked to the COPD exacerbation pathophysiology. These findings point toward a multisystem approach, an Internal Medicine hallmark, when managing a COPD exacerbation patient with various comorbidities. More studies are needed to further understand the role of these findings namely in severity stratification and therapeutic guidance. ■

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Direito à Privacidade e Consentimento Informado: Os autores declaram que nenhum dado que permita a identificação do doente aparece neste artigo.

Protecção de Seres Humanos e Animais: Os autores declaram que não foram realizadas experiências em seres humanos ou animais.

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